

RECEIVED  
SEP 20 2000

TECHNICAL CENTER 1600/2900

- (ii) crystalline particles of a therapeutic agent which is poorly soluble in said liquid, and
- (iii) at least one surface modifier adsorbed on the surface of the crystalline therapeutic agent particles, wherein the crystalline agent/surface modifier particles have an average particle size of less than about 1000 nm.

11. The method of claim 10, wherein the crystalline particles of a poorly soluble therapeutic agent have an average particle size of less than about 400 nm.

12. The method of claim 11, wherein the crystalline particles of a poorly soluble therapeutic agent have an average particle size of less than about 300 nm.

A 13. The method of claim 12, wherein the crystalline particles of a poorly soluble therapeutic agent have an average particles size of less than about 100 nm.

14. The method of claim 10, wherein the surface modifier is selected from the group consisting of gelatin, casein, gum acacia, cholesterol, tragacanth, stearic acid, benzalkonium chloride, calcium stearate, glycerol monostearate, cetostearyl alcohol, cetomacrogol emulsifying wax, sorbitan esters, polyoxyethylene alkyl ethers, polyoxyethylene castor oil derivatives, polyethylene glycols, polyoxyethylene stearates, colloidal silicon dioxide, phosphates, sodium dodecylsulfate, carboxymethylcellulose calcium, carboxymethylcellulose sodium, methylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose phthalate, noncrystalline cellulose, magnesium aluminum silicate, triethanolamine, polyvinyl alcohol, polyvinylpyrrolidone, tyloxapol, a polymer, a polyoxamine, dextran, lecithin, a dialkylester of sodium sulfosuccinic acid, sodium lauryl sulfate, an alkyl aryl polyether sulfonate, a polyoxyethylene sorbitan fatty acid ester, a mixture of sucrose stearate and sucrose distearate,  $C_{18}H_{37}CH_2(CON_9CH_3)CH_2(CHOH)_4(CH_2H)_2$ , a sulfated block copolymer of ethylene oxide and propylene oxide, and a triblock copolymer of the structure - (PEO) (PBO) (PEO) - having a molecular weight of about 3800 to about 5000.

15. The method of claim 10 comprising at least two surface modifiers.
16. The method of claim 10, wherein the surface modifier is present at an amount of from about 0.1% to about 90% (w/w), based upon the total weight of the combined therapeutic agent and surface modifier.
17. The method of claim 16, wherein the surface modifier is present at an amount of from about 1% to about 75% (w/w), based upon the total weight of the combined therapeutic agent and surface modifier.
18. The method of claim 17, wherein the surface modifier is present at an amount of from about 20% to about 60% (w/w), based upon the total weight of the combined therapeutic agent and surface modifier.
- A 19. The method of claim 10, wherein the therapeutic agent is selected from the group consisting of analgesics, anti-inflammatory agents, anthelmintics, anti-arrhythmic agents, antibiotics, anticoagulants, antidepressants, antidiabetic agents, antiepileptics, antihistamines, antihypertensive agents, antimuscarinic agents, antimycobacterial agents, antineoplastic agents, immunosuppressants, antithyroid agents, antiviral agents, anxiolytic sedatives, astringents, beta-adrenoceptor blocking agents, blood products and substitutes, cardiac inotropic agents, corticosteroids, cough suppressants, diuretics, dopaminergics, haemostatics, immunological agents, lipid regulating agents, muscle relaxants, parasympathomimetics, parathyroid calcitonin and biphosphonates, prostaglandins, radio-pharmaceuticals, sex hormones, anti-allergic agents, stimulants, anorectics, sympathomimetics, thyroid agents, vasodilators, and xanthines.
20. The method of claim 10, wherein the therapeutic agent is beclomethasone dipropionate.

21. The method of claim 10, wherein the therapeutic agent is present in the liquid medium at an amount of from about 0.1% to about 60% (w/w), based on the total weight of the therapeutic agent and surface modifier.

22. The method of claim 21, wherein the therapeutic agent is present in the liquid medium at an amount of from about 5% to about 30% (w/w), based on the total weight of the therapeutic agent and surface modifier.

23. The method of claim 10, wherein said liquid is selected from the group consisting of water, aqueous salt solutions, safflower oil, ethanol, t-butanol, hexane, and glycol.

24. The method of claim 10, wherein a jet nebulizer is used to form the aerosol.

25. The method of claim 10, wherein an ultrasonic nebulizer is used to form the aerosol.

26. The method of claim 10, wherein a respiratory illness is treated, which is selected from the group consisting of asthma, emphysema, respiratory distress syndrome, chronic bronchitis, cystic fibrosis, acquired immune deficiency syndrome (AIDS), and AIDS-related pneumonia.

27. The method of claim 10, wherein the aerosol further comprises a liquid propellant.

28. A method of delivering an aerosol to the lungs of a mammal comprising administering a nanoparticulate aerosol composition comprising:

- (a) liquid droplet having a particle size of less than about fifty microns in diameter; and
- (b) the liquid droplets comprise:
- (i) a liquid,

- Sub  
part*
- (ii) crystalline particles of a therapeutic agent which is poorly soluble in said liquid; and
  - (iii) at least one surface modifier adsorbed on the surface of the crystalline therapeutic agent particles, wherein the crystalline agent/surface modifier particles have an average particle size of less than about 1000 nm.

29. The method of claim 28, wherein the crystalline particles of a poorly soluble therapeutic agent have an average particle size of less than about 400 nm.

30. The method of claim 29, wherein the crystalline particles of a poorly soluble therapeutic agent have an average particle size of less than about 300 nm.

*A*

31. The method of claim 30, wherein the crystalline particles of a poorly soluble therapeutic agent have an average particles size of less than about 100 nm.

32. The method of claim 28, wherein the surface modifier is selected from the group consisting of gelatin, casein, gum acacia, cholesterol, tragacanth, stearic acid, benzalkonium chloride, calcium stearate, glycerol monostearate, cetostearyl alcohol, cetomacrogol emulsifying wax, sorbitan esters, polyoxyethylene alkyl ethers, polyoxyethylene castor oil derivatives, polyethylene glycols, polyoxyethylene stearates, colloidal silicon dioxide, phosphates, sodium dodecylsulfate, carboxymethylcellulose calcium, carboxymethylcellulose sodium, methylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose phthalate, noncrystalline cellulose, magnesium aluminum silicate, triethanolamine, polyvinyl alcohol, polyvinylpyrrolidone, tyloxapol, a polymer, a polyoxamine, dextran, lecithin, a dialkylester of sodium sulfosuccinic acid, sodium lauryl sulfate, an alkyl aryl polyether sulfonate, a polyoxyethylene sorbitan fatty acid ester, a mixture of sucrose stearate and sucrose distearate,  $C_{18}H_{37}CH_2(CON_9CH_3)CH_2(CHOH)_4(CH_2H)_2$ , a sulfated block copolymer of ethylene oxide and propylene oxide, and a triblock copolymer of the structure - (PEO) (PBO) (PEO) - having a molecular weight of about 3800 to about 5000.

33. The method of claim 28 comprising at least two surface modifiers.

34. The method of claim 28, wherein the surface modifier is present at an amount of from about 0.1% to about 90% (w/w), based upon the total weight of the combined therapeutic agent and surface modifier.

35. The method of claim 34, wherein the surface modifier is present at an amount of from about 1% to about 75% (w/w), based upon the total weight of the combined therapeutic agent and surface modifier.

A 36. The method of claim 35, wherein the surface modifier is present at an amount of from about 20% to about 60% (w/w), based upon the total weight of the combined therapeutic agent and surface modifier.

37. The method of claim 28, wherein the therapeutic agent is selected from the group consisting of analgesics, anti-inflammatory agents, anthelmintics, anti-arrhythmic agents, antibiotics, anticoagulants, antidepressants, antidiabetic agents, antiepileptics, antihistamines, antihypertensive agents, antimuscarinic agents, antimycobacterial agents, antineoplastic agents, immunosuppressants, antithyroid agents, antiviral agents, anxiolytic sedatives, astringents, beta-adrenoceptor blocking agents, blood products and substitutes, cardiac inotropic agents, corticosteroids, cough suppressants, diuretics, dopaminergics, haemostatics, immunological agents, lipid regulating agents, muscle relaxants, parasympathomimetics, parathyroid calcitonin and biphosphonates, prostaglandins, radio-pharmaceuticals, sex hormones, anti-allergic agents, stimulants, anorectics, sympathomimetics, thyroid agents, vasodilators, and xanthines.

38. The method of claim 28, wherein the therapeutic agent is beclomethasone dipropionate.

39. The method of claim 28, wherein the therapeutic agent is present in the liquid medium at an amount of from about 0.1% to about 60% (w/w), based on the total weight of the therapeutic agent and surface modifier.

40. The method of claim 39, wherein the therapeutic agent is present in the liquid medium at an amount of from about 5% to about 30% (w/w), based on the total weight of the therapeutic agent and surface modifier.

41. The method of claim 28, wherein said liquid is selected from the group consisting of water, aqueous salt solutions, safflower oil, ethanol, t-butanol, hexane, and glycol.

42. The method of claim 28, wherein a jet nebulizer is used to form the aerosol.

43. The method of claim 28, wherein an ultrasonic nebulizer is used to form the aerosol.

44. The method of claim 28, wherein a respiratory illness is treated, which is selected from the group consisting of asthma, emphysema, respiratory distress syndrome, chronic bronchitis, cystic fibrosis, acquired immune deficiency syndrome (AIDS), and AIDS-related pneumonia.

45. The method of claim 28, wherein the aerosol further comprises a liquid propellant.--

---